CLAIM LISTING

1. (Original) A pharmaceutical composition comprising a biologically active agent and a mucosal delivery-enhancing effective amount of a permeabilizing peptide that reversibly enhances mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in a mammalian subject, wherein said peptide effectively inhibits homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin.

2. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

3. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 6-15 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

4. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

5. (Original) The pharmaceutical composition of claim 4, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

6. (Original) The pharmaceutical composition of claim 5, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more conservative amino acid substitutions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

7. (Original) The pharmaceutical composition of claim 5, wherein said permeabilizing peptide is a human JAM peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the same human JAM protein, said mutation(s) corresponding to a structural feature identified in a different human JAM protein or a homologous JAM protein found in a different species.

8. (Original) The pharmaceutical composition of claim 5, wherein said permeabilizing peptide is a human JAM-1 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the human JAM-1 protein, said mutation(s) corresponding to a structural feature identified in a human JAM-2 or JAM-3 protein.

9. (Original) The pharmaceutical composition of claim 5, wherein said permeabilizing peptide is a human JAM-1, JAM-2, or JAM-3 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of a human JAM-1, JAM-2, or JAM-3 protein, respectively, said mutation(s) corresponding to a structural feature identified in a murine, rat, or bovine JAM-1, JAM-2 or JAM-3 protein, respectively.

10. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 59), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62), or a human occludin peptide GVNPTAQSS

(SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

11. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

12. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from a small molecule drug, a peptide, a protein, and a vaccine agent.

13. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from an opiod, opiod antagonist, corticosterone, anti-inflammatory, androgen, estrogen, progestin, muscle relaxant, vasodilator, antihistamine, histamine receptor site blocking agent, antitussive, antiepileptic, anti-fungal agent, antibacterial agent, cancer therapeutic agent, antioxidant, antiarrhythmic agents, antihypertensive agent, monoclonal or polyclonal antibody, anti-sense oligonucleotide, and an RNA, DNA or viral vector comprising a gene encoding a therapeutic peptide or protein.

14. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from a therapeutic protein or peptide.

15. (Original) The pharmaceutical composition of claim 14, wherein said therapeutic protein or peptide is selected from tissue plasminogen activator (TPA), epidermal growth factor

(EGF), fibroblast growth factor (FGF-acidic or basic), platelet derived growth factor (PDGF), transforming growth factor (TGF-alpha or beta), vasoactive intestinal peptide, tumor necrosis factor (TGF), hypothalmic releasing factors, prolactin, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), parathyroid hormone (PTH), follicle stimulating hormone (FSF), luteinizing hormone releasing (LHRH), endorphins, glucagon, calcitonin, oxytocin, carbetocin, aldoetecone, enkaphalins, somatostin, somatotropin, somatomedin, gonadotrophin, estrogen, progesterone, testosterone, alpha-melanocyte stimulating hormone, non-naturally occurring opiods, lidocaine, ketoprofen, sufentainil, terbutaline, droperidol, scopolamine, gonadorelin, ciclopirox, olamine, buspirone, calcitonin, cromolyn sodium or midazolam, cyclosporin, lisinopril, captopril, delapril, cimetidine, ranitidine, famotidine, superoxide dismutase, asparaginase, arginase, arginine deaminease, adenosine deaminase ribonuclease, trypsin, chemotrypsin, papain, bombesin, substance P, vasopressin, alpha-globulins, transferrin, fibrinogen, beta-lipoproteins, beta-globulins, prothrombin, ceruloplasmin, $alpha_2$-glycoproteins, $alpha_2$-globulins, fetuin, alpha-lipoproteins, alpha-globulins, albumin, and prealbumin.

16. (Original) The pharmaceutical composition of claim 14, wherein said therapeutic protein or peptide is effective as a hematopoietic agent, cytokine agent, antiinfective agent, antidementia agent, antiviral agent, antitumoral agent, antipyretic agent, analgesic agent, antiinflammatory agent, antiulcer agent, antiallergic agent, antidepressant agent, psychotropic agent, cardiotonic agent, antiarrythmic agent, vasodilator agent, antihypertensive agent, antidiabetic agent, anticoagulant agent, cholesterol-lowering agent, hormone agent, anti-osteoporosis agent, antibiotic agent, vaccine agent, or bacterial toxoid.

17. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent and said permeabilizing peptide are administered in combination with one or more mucosal delivery-enhancing agents selected from:

(a) an aggregation inhibitory agent;

(b) a charge modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced mucosal delivery, wherein said one or more mucosal delivery-enhancing agents comprises any one or any combination of two or more of said mucosal delivery-enhancing agents recited in (a)-(k), and wherein the formulation of said biologically active agent with said mucosal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a mucosal surface of a mammalian subject.

18. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

19. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 6-15 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

20. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

21. (Original) The pharmaceutical composition of claim 20, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian occludin protein.

22. (Original) The pharmaceutical composition of claim 21, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more conservative amino acid substitutions compared to said corresponding reference sequence of the mammalian occludin protein.

23. (Original) The pharmaceutical composition of claim 21, wherein said permeabilizing peptide is a human occludin peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the same human occludin protein, said mutation(s) corresponding to a structural feature identified in a different human occludin protein or a homologous occludin protein found in a different species.

24. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

25. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 6-15 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

26. (Original) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular

domain of a mammalian claudin protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

27. (Original) The pharmaceutical composition of claim 26, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian claudin protein.

28. (Original) The pharmaceutical composition of claim 27, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more conservative amino acid substitutions compared to said corresponding reference sequence of the mammalian claudin protein.

29. (Original) The pharmaceutical composition of claim 27, wherein said permeabilizing peptide is a human claudin peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the same human claudin protein, said mutation(s) corresponding to a structural feature identified in a different human claudin protein or a homologous claudin protein found in a different species.

30. (Original) The pharmaceutical composition of claim 1, formulated for intranasal administration.

31. (Original) The pharmaceutical composition of claim 1, formulated as an intranasal spray or powder.

32. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent and said permeabilizing peptide formulated for intranasal administration with one or more intranasal delivery-enhancing agents selected from:

(a) an aggregation inhibitory agent;

(b) a charge modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced intranasal delivery, wherein said one or more intranasal delivery-enhancing agents comprises any one or combination of two or more of said intranasal delivery-enhancing agents recited in (a)-(k), and wherein the formulation of said biologically active agent with said one or more intranasal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a nasal mucosal surface of a mammalian subject.

33. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a peak concentration (C_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 25% or greater as compared to a peak concentration of the biologically active agent following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

34. (Original) The pharmaceutical composition of claim 33, wherein said composition following mucosal administration to said subject yields a peak concentration (C_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 50% or greater as compared to a peak concentration of the biologically active agent in the blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

35. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 25% or greater compared to an AUC of the biologically active agent in blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

36. (Original) The pharmaceutical composition of claim 35, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 50% or greater compared to an AUC of the biologically active agent in blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

37. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a time to maximal plasma concentration (t_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.1 to 1.0 hours.

38. (Original) The pharmaceutical composition of claim 37, wherein said composition following mucosal administration to said subject yields a time to maximal plasma concentration (t_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.2 to 0.5 hours.

39. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 10% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

40. (Original) The pharmaceutical composition of claim 39, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 20% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

41. (Original) The pharmaceutical composition of claim 39, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 40% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

42. (Original) The pharmaceutical composition of claim 1, wherein the biologically active agent is effective for treatment of sexual dysfunction.

43. (Original) The pharmaceutical composition of claim 42, wherein the biologically active agent is effective for treatment of male erectile sexual dysfunction.

44. (Original) The pharmaceutical composition of claim 43, wherein the biologically active agent is effective for treatment of female sexual dysfunction.

45. (Original) The pharmaceutical composition of claim 42, wherein the biologically active agent is a dopamine receptor agonist.

46. (Original) The pharmaceutical composition of claim 44, wherein the biologically active agent is apomorphine or a pharmaceutically acceptable salt or derivative thereof.

47. (Original) The pharmaceutical composition of claim 44, wherein the biologically active agent is selected from interferon-α, interferon-β, human growth hormone (HGH), insulin, heparin, nerve growth factor (NGF), erythropoietin (EPO), acetylcholinesterase (ACTH), amyloid peptide, beta-sheet blocking peptide, natriuretic peptide, ketoprofen, and oleamide.

48. (Withdrawn) A method for treating or preventing a disease or condition in a mammalian subject amenable to treatment by therapeutic administration of a biologically active, therapeutic agent, comprising mucosally administering to said subject a pharmaceutical formulation comprising a mucosal delivery-enhancing effective amount of a permeabilizing peptide that reversibly enhances mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in the subject, wherein said peptide effectively inhibits homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin, and coordinately administering the biologically active, therapeutic agent.

49. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 53), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62), or a human occludin peptide GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

50. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

51. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide has a sequence selected from VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), or EDTGTYTCM (SEQ ID NO: 9).

52. (Withdrawn) The method of claim 48, wherein said mucosal administration involves delivery of said formulation to a nasal mucosal surface of said subject.

53. (Withdrawn) The method of claim 48, wherein the dopamine receptor agonist is apomorphine or a pharmaceutically acceptable salt or derivative thereof.

54. (Withdrawn) A coordinate administration method for enhanced mucosal delivery of a biologically active agent comprising:

administering to a mammalian subject an mucosally effective amount of at least one biologically active agent in a coordinate administration protocol with a mucosal delivery-enhancing effective amount of a permeabilizing peptide that reversibly enhances mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in the subject, wherein said peptide effectively inhibits homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin.

55. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is administered before, simultaneous with, or following coordinate administration of said permeabilizing peptide.

56. (Withdrawn) The coordinate administration method of claim 55, wherein said permeabilizing peptide is administered prior to administration of said biologically active agent by an effective pre-administration period to yield enhancement of mucosal epithelial paracellular transport.

57. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered essentially simultaneously in a mixture or contemporaneously applied, separate formulations.

58. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

59. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 6-15 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

60. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

61. (Withdrawn) The coordinate administration method of claim 60, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

62. (Withdrawn) The coordinate administration method of claim 60, wherein said permeabilizing peptide is a human JAM-1 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the human JAM-1 protein, said mutation(s) corresponding to a structural feature identified in a human JAM-2 or JAM-3 protein.

63. (Withdrawn) The coordinate administration method of claim 60, wherein said permeabilizing peptide is a human JAM-1, JAM-2, or JAM-3 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of a human JAM-1, JAM-2, or JAM-3 protein, respectively, said mutation(s) corresponding to a structural feature identified in a murine, rat, or bovine JAM-1, JAM-2 or JAM-3 protein, respectively.

64. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO:58), GILRDFYSPL (SEQ ID NO:53), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62), or a human occludin peptide GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

65. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

66. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is selected from a small molecule drug, a peptide, a protein, and a vaccine agent.

67. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is selected from an opiod, opiod antagonist, corticosterone, anti-inflammatory, androgen, estrogen, progestin, muscle relaxant, vasodilator, antihistamine, histamine receptor site blocking agent, antitussive, antiepileptic, anti-fungal agent, antibacterial agent, cancer therapeutic agent, antioxidant, antiarrhythmic agents, antihypertensive agent, monoclonal or polyclonal antibody, anti-sense oligonucleotide, and an RNA, DNA or viral vector comprising a gene encoding a therapeutic peptide or protein.

68. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is a therapeutic protein or peptide selected from tissue plasminogen activator (TPA), epidermal growth factor (EGF), fibroblast growth factor (FGF-acidic or basic), platelet derived growth factor (PDGF), transforming growth factor (TGF-alpha or beta), vasoactive intestinal peptide, tumor necrosis factor (TGF), hypothalmic releasing factors, prolactin, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), parathyroid hormone (PTH), follicle stimulating hormone (FSF), luteinizing hormone releasing (LHRH), endorphins, glucagon, calcitonin, oxytocin, carbetocin, aldoctecone, enkaphalins, somatostin, somatotropin, somatomedin, gonadotrophin, estrogen, progesterone, testosterone, alpha-melanocyte stimulating hormone, non-naturally occurring opiods, lidocaine, ketoprofen, sufentainil, terbutaline, droperidol, scopolamine, gonadorelin, ciclopirox, olamine, buspirone,

calcitonin, cromolyn sodium or midazolam, cyclosporin, lisinopril, captopril, delapril, cimetidine, ranitidine, famotidine, superoxide dismutase, asparaginase, arginase, arginine deaminase, adenosine deaminase ribonuclease, trypsin, chemotrypsin, papain, bombesin, substance P, vasopressin, alpha-globulins, transferrin, fibrinogen, beta-lipoproteins, beta-globulins, prothrombin, ceruloplasmin, alpha$_2$-glycoproteins, alpha$_2$-globulins, fetuin, alpha-lipoproteins, alpha-globulins, albumin, and prealbumin.

69. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is a therapeutic protein or peptide effective as a hematopoietic agent, cytokine agent, antiinfective agent, antidementia agent, antiviral agent, antitumoral agent, antipyretic agent, analgesic agent, antiinflammatory agent, antiulcer agent, antiallergic agent, antidepressant agent, psychotropic agent, cardiotonic agent, antiarrythmic agent, vasodilator agent, antihypertensive agent, antidiabetic agent, anticoagulant agent, cholesterol-lowering agent, hormone agent, anti-osteoporosis agent, antibiotic agent, vaccine agent, or bacterial toxoid.

70. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered in combination with one or more mucosal delivery-enhancing agents selected from:

(a) an aggregation inhibitory agent;

(b) a charge modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid

or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced mucosal delivery, wherein said one or more mucosal delivery-enhancing agents comprises any one or any combination of two or more of said mucosal delivery-enhancing agents recited in (a)-(k), and wherein the formulation of said biologically active agent with said mucosal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a mucosal surface of a mammalian subject.

71. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

72. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

73. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

74. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein or comprises an amino acid sequence that exhibits at

least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

75. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered intranasally.

76. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are coordinately administered or formulated in combination with one or more intranasal delivery-enhancing agents selected from:

(a) an aggregation inhibitory agent;

(b) a charge modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced intranasal delivery, wherein said one or more intranasal delivery-enhancing agents comprises any one or

combination of two or more of said intranasal delivery-enhancing agents recited in (a)-(k), and wherein the coordinate administration or combinatorial formulation of said biologically active agent with said one or more intranasal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a nasal mucosal surface of a mammalian subject.

77. (Withdrawn) The coordinate administration method of claim 54, which yields a peak concentration (C_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 25% or greater as compared to a peak concentration of the biologically active agent following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

78. (Withdrawn) The coordinate administration method of claim 54, which yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 25% or greater compared to an AUC of the biologically active agent in blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

79. (Withdrawn) The coordinate administration method of claim 54, which yields a time to maximal plasma concentration (t_{max}) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.2 to 0.5 hours.

80. (Withdrawn) The coordinate administration method of claim 54, which yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 10% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

81. (Withdrawn) The coordinate administration method of claim 54, wherein the biologically active agent is selected from interferon-α, interferon-β, human growth hormone (HGH), insulin, heparin, nerve growth factor (NGF), erythropoietin (EPO), acetylcholinesterase (ACTH), amyloid peptide, beta-sheet blocking peptide, natriuretic peptide, ketoprofen, and oleamide.

82. (Original) A permeabilizing peptide for enhancing mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in a mammalian subject by effectively inhibiting homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin, said permeabilizing peptide comprising from about 4-25 contiguous amino acids of a wild-type sequence of an extracellular domain of a mammalian JAM-1, JAM-2, JAM-3, occludin or claudin protein, or an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of about 4-25 contiguous amino acids of a wild-type sequence of an extracellular domain of a mammalian JAM-1, JAM-2, JAM-3, occludin or claudin protein.

83. (Original) The peptide of claim 82, which comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

84. (Original) The peptide of claim 83, which exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

85. (Original) The peptide of claim 84, which exhibits one or more conservative amino acid substitutions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

86. (Original) The peptide of claim 84, which is a human JAM peptide exhibiting one or more amino acid mutations in comparison to a corresponding wild-type sequence of the same human JAM protein, said mutation(s) corresponding to a structural feature identified in a different human JAM protein or a homologous JAM protein found in a different species.

87. (Original) The peptide of claim 84, which is a human JAM-1 peptide.

88. (Original) The peptide of claim 84, which is a human JAM-1 peptide exhibiting one or more amino acid mutations in comparison to a corresponding wild-type sequence of the

human JAM-1 protein, said mutation(s) corresponding to a structural feature identified in a human JAM-2 or JAM-3 protein.

89. (Original) The peptide of claim 84, which is a human JAM-1, JAM-2, or JAM-3 peptide.

90. (Original) The peptide of claim 84, which is a human JAM-1, JAM-2, or JAM-3 peptide exhibiting one or more amino acid mutations in comparison to a corresponding wild-type sequence of a human JAM-1, JAM-2, or JAM-3 protein, respectively, said mutation(s) corresponding to a structural feature identified in a murine, rat, or bovine JAM-1, JAM-2 or JAM-3 protein, respectively.

91. (Original) The peptide of claim 84, which is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 53), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62), or a human occludin peptide GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

92. (Original) The peptide of claim 84, which is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

RESPONSE

Claims 1-92 are pending in the subject application. The election, described below, identifies Claims 1-17, 42-45 and 47 for further prosecution.

Examiner requires Applicant to elect among more than 536,000,000 inventions (see page 11 "within Inventions VI-XLV claims 17, 32, 70 and 76 define approximately 536 million inventions"), leaving Applicant in an untenable position. Applicant must either concede that the claimed invention is narrow in scope, or show the Patent Office's ruling violates the Patent Office rules and policies.

If Applicant pursues the former course, filing fees alone are staggering: these will exceed the GNP of Sweden and Argenina *combined*. At a filing rate of ten applications per day, Applicant would need 200,000 man-lifetimes merely to lodge these in the Patent Office. If Applicant decided to forgo even a small fraction of these (10 million applications, say), Applicant could risk patent disclaimer in an attempt to broaden the literal scope of issued claims to prevent sale of a competitor's knock-off product.

On the other hand, given the complexity of the restriction requirement, any attempt to argue that it is improper, even in a small part, could and likely will create future estoppel impacting the patentability and ultimately the validity of the claimed subject matter.

Restriction practice is inherently an arbitrary process. Two restriction requirements issued on the same case at the same time by two different Examiners will necessarily be based on different theories and break up the inventions in completeley different ways. In the instant case, two restriction requirements based on completely different theories were issued by the same Examiner within nine months of each other. Such diversity in outcome reveals its arbitrariness.

The first restriction requirement was exceedingly complex, involve abstruse reasoning and numerous assumptions about the invention. Applicant simply did not have the legal resources to respond fully to every statement of Examiner. Applicant elected invention and species properly, based on Applicant's best understanding of the requirements and after consulting with several attorneys. Even so, Applicant received a second office action requiring further election among species, and further study of the restriction requirements. Now, months later, without any change in the application, Applicant received a new office action with the original restriction requirement withdrawn, and a new one issued. This file history naturally

prejudices Applicant for concessions it made in its previous response. Even though no new papers were filed in the application, Examiner now finds more than 536 million inventions previously overlooked by the Patent Office.

Filing a second restriction requirement after withdrawing a first violates patent office rules, and is arbitrary and capricious. It also deals an unfair blow toApplicant causing excessive waste of judicial resources and creating prejudice to his entitlement to obtain patent rights in exchange for disclosure of trade secrets and innovation to the public.

The relevant Patent Office rule, Rule 142, does not provide for issuance of a second restriction requirement after a response to a previous restriction requirement, subsequently withdrawm. Rule 142(a) states only "[s]uch requirement will normally be made before any action of the merits; however it may be made at any time before final action." MPEP 811.02 (2005) interprets Rule 142(a) and states "a second [restriction] requirement may be made when it *becomes* proper, even though there was a prior requirement with which applicant complied" (emphasis added). In the instant case, since no intervening amendments to the claims were made, conditions could not exist to cause the second requirement to *become* proper. In the absence of just cause, a second restriction requirement is arbitrary and capricious.

Examiner appears unaware of the potential prejudice Applicant's response to the first requirement created. A prosecution file with two requirements, equally byzantine in their complexity, creates potential for misinterpreting any response of Applicant. It is unfair for the Patent Office to subject Applicant to such prejudice, particularly at the start of prosecution. Under normal circumstances, restriction requirements are somewhat procedural and simple enough for Applicant to decide after a few minutes discussion on the phone based on Examiner brief explanation. In this case, Examiner issued two requirements: each required hours of study and a detailed written response, which in the first instance was unintentionally incomplete for supposedly failing to see all the nuances of the requirements.

It is commonly believed that Congress gave the Patent Office the power of restricting applications into "two or more independent and distinct inventions" (35 U.S.C. § 121 (2002)) solely to allow it a means of creating more revenue based on examination fees. In this instance, this power has been misused. It appears that the patent office expects Applicant to

singlehandedly supply it with revenue for careers of hundreds of patent examiners and attorneys. This is unreasonable.

Examiner required restriction to Groups I to XLV solely based on differences in classification, and in most cases differences in subclassification. Applicant respectfully traverses. Examiner has not established a *prima facie* case for restriction. Examiner failed to provide an appropriate explanation as to why "each distinct subject has attainted recognition in the art as a separate subject for inventive effort, and also a separate field of search" (MPEP § 808.02).

If based on classification, the Patent Office has held that classification schemes are to assist in searches, and "cannot have a conclusive bearing on a question of division in a particular case" (*Ex parte Pratt*, 46 USPQ 338, 339 (1930)). Examiner stated that inventions VI-XXV (including claims 2-23 and 30-47) are all "directed to related compositions." For his reasons for restriction, Examiner states without evidence or citation that different peptides, being structurally distinct, would be expected to have different effects and modes of operation. Applicant respectfully disagrees. Examiner's basis in restriction fails to demonstrate which inventions are distinct. The peptides are all described as permeabilizing peptides that reversibly enhances epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in a mammalian subject. Applicant supplies ample data to demonstrate this unity of function. Examiner contradicts this aspect of the application by his statement that he expects these peptides to have different effects and modes of operation. Applicant nowhere claims subject matter that depends on effects other than enhancement of mucosal delivery, without being limited to any particular mode of operation. Accordingly, the field of search is the same for inventions VI-XXV.

Examiner also asserts that compositions and compounds related to each other as combination and subcombination, respectfully and so inventions embodying these must be restricted. Applicant respectfully traverses. Examiner has not explained how these inventions differ with respect to status in the art or field of search. While the classification index may differs, these differences appear de minimus: it is by no means apparent how these can be used to restrict inventions. Examiner at page 11 produces an arbitrary reason – that "[t]he subcombination [of JAM-4 and VE-JAM?] has separate utility as modulators of inflammation or

as Lewis antigens" – without any factual basis or context. It is entirely unclear what that has to do with Examiner's restriction requirement. Moreover, the relevance of Lewis antigens or imflammatory reagents have to do with subcombinations seems to be altogether missing.

That inventions VI-XXV are unified is belied by Examiner's statement that the restriction requirements among inventions 6-17 and 26-37 are subject to the nonallowance of certain linking claims, and would otherwise be withdrawn.

Notwithstanding the traversal articulated above, Applicant elects invention VII, and immediately requests rejoinder of this invention VII with inventions VIII and IXX, also drawn to pharmaceutical compositions comprising JAM-1 peptides. Applicant's election corresponds to claims 2-17, 42-45 and 47, as well as linking claim 1. In response to the further restriction requirement, Applicant elects, for claim 17, a membrane penetration-enhancing agent selected to be a cyclodextrin or beta-cyclodextrin derivative. These elections are made without waiver of any and all rights to rejoinder at any time prior to issuance of a patent.

Reconsideration of the election requirements and examination of the elected claims and subject matter is respectfully requested.

Respectfully submitted,

Respectfully Submitted,

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